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Flow-Mediated Synthesis of Boc, Fmoc, and Ddiv Monoprotected Diamines

Citation for published version:

Jong, T & Bradley, M 2015, 'Flow-Mediated Synthesis of Boc, Fmoc, and Ddiv Monoprotected Diamines', *Organic letters*, vol. 17, no. 3, pp. 422-425. <https://doi.org/10.1021/ol503343b>

Digital Object Identifier (DOI):

[10.1021/ol503343b](https://doi.org/10.1021/ol503343b)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Organic letters

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Flow Mediated Synthesis of Boc, Fmoc and Ddiv Mono-Protected Diamines

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1. General Experimental

All solvents and reagents were obtained from commercial suppliers and used without purification, unless otherwise stated. The synthesis of DdivOH was modified from literature procedure (Kellam, B.; Chan, W. C.; Chhabra, S. R.; Bycroft, B. W. *Tetrahedron Letters* **1997**, 38, 5391-5394).

^1H and ^{13}C NMR spectra were recorded on an automated Bruker AVA 500 (500 and 125 MHz, respectively) in the indicated solvents at 298 K. Chemical shifts (δ) are quoted in parts per million (ppm) relative to the residual solvent and all coupling constants (J) were measured in Hertz (Hz). Electrospray mass spectrometry (ESI-MS) analysis was performed on an Agilent 1100 series LC-MS system. Mass spectra were acquired via a VG Platform Single Quadrupole Electrospray Ionisation (ESI) mass spectrometer. High Resolution Mass Spectrometry (HR-MS) was performed using Bruker 3.0 T Apex II spectrometer.

Analytical HPLC was conducted on an Agilent 1100 series HPLC system coupled to a Polymer Lab PL-ELS 1000 Evaporative Light Scattering (ELS) detector with UV detection at 220, 254, 260, 282 and 495 nm. Supelco's Discovery[®] C18 (50 mm x 2.1 mm x 5 μm) column was used. Infrared (IR) spectra were recorded on a Fourier Transform IR Bruker Tensor 27 spectrometer. All samples were run neat and frequencies were reported in cm^{-1} . Only frequencies corresponding to significant functional groups are reported.

2. Flow Instrumentation

The flow experiments were performed on a self-assembled continuous flow set-up (Figure S1–S2). Two HPLC pumps (Knauer Smartline Pump 100) were used to deliver the reactants continuously into the flow reactor. A PEEK T-mixer (0.80 mm internal bore) was used to mix two separate feed streams and the mixture was channelled into the flow reactor. The coil reactor was made of PTFE tubing (0.50 mm I.D.) with an internal volume of 2.0 or 4.0 mL. In order to perform reactions at elevated temperatures, an adjustable back-pressure regulator (BPR) (PEEK housing, spring-loaded FFKM diaphragm, polyimide membrane, 1–20 bar operating pressure) was installed to pressurise the flow system. Standard HPLC fittings were used to connect each individual component to create a fully functional reaction platform.



Figure S1 Continuous flow reaction system used in this study.

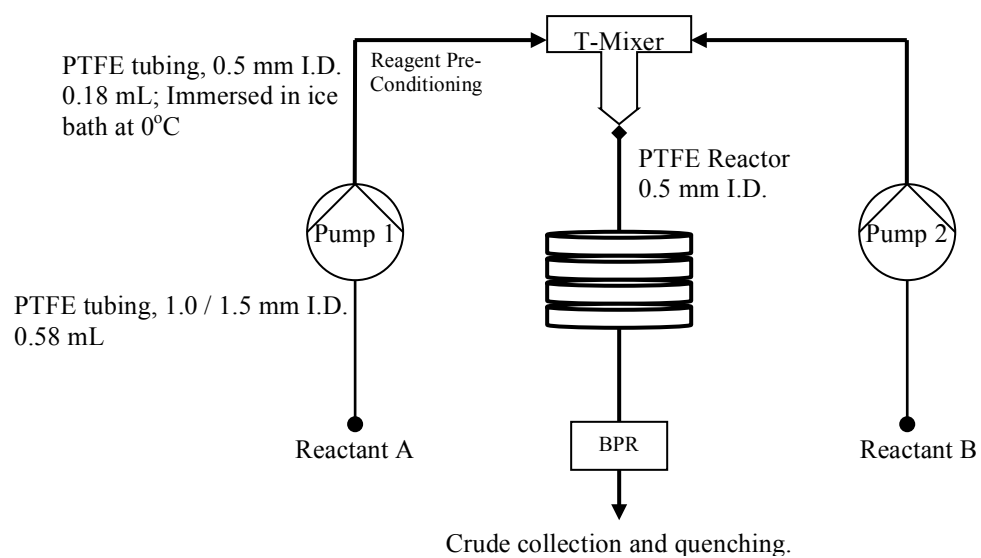
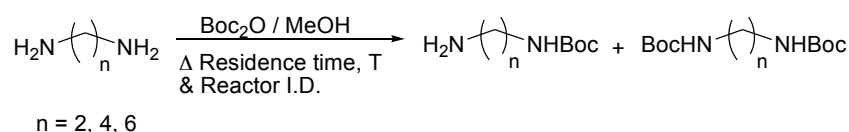


Figure S2 General set-up of the continuous flow reaction system.

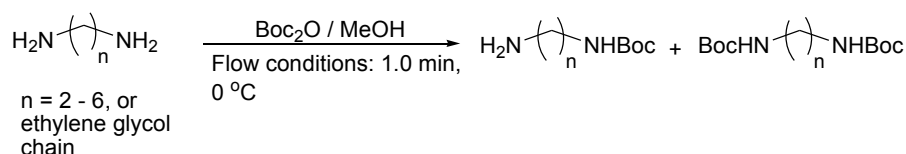
3. Flow Mediated Mono-Boc Carbamation

Reaction Screening



1,2-diaminoethane, 1,4-diaminobutane or 1,6-diaminohexane (0.1 M, 20 mL) and Boc_2O (0.1 M, 20 mL) in MeOH were fed continuously into a PTFE reactor (0.5, 1.0 or 1.5 mm I.D., 2.0 mL total volume) immersed in a water bath (0 or 25 °C). The reactants were fed into their respective PTFE channels (0.5 mm I.D., 0.18 mL volume) immersed in a temperature adjusted bath. The reactants converged in the T-mixer, and the stoichiometry and residence time of the reaction were determined by adjusting the pump flow rates. The reaction stream (40 mL) was collected at steady state after 1.5 reactor volume, into a flask filled with MeOH (80 mL, -10 °C) containing an excess of silica-based Trisamine scavenger (Biotage's Isolute Si-Trisamine, 1.3 g, 2.0 mmol; assuming 50% mono-Boc carbamation efficiency). The solution was filtered and the filtrate concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, 9:1 DCM–MeOH with 0.1% TEA).

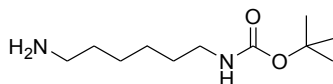
General Procedure



Diamines (0.1 M, 100 mL) and Boc_2O (0.2 M, 100 mL) in MeOH were fed continuously into a PTFE reactor (0.5 mm I.D., 4.0 mL total volume) immersed in an ice bath (0 °C). The reactants were fed into their respective PTFE channels (0.5 mm I.D., 0.18 mL volume) immersed in a temperature adjusted bath. The reactants converged in the T-mixer and the total flow rate of reaction stream was fixed at 4.0 mLmin⁻¹ to give a residence time of 1.0 min. The reaction stream (200 mL) was collected at steady state after 1.5 reactor volume, into a flask filled with cold MeOH (200 mL, -10 °C) containing an excess of silica-based Trisamine scavenger (Biotage's Isolute Si-Trisamine, 6.00 g, 9.4 mmol; assuming 50% mono-Boc carbamation efficiency) under rigorous stirring. The solution was filtered and the filtrate

concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, 9:1 DCM–MeOH with 0.1% TEA) to give the mono-Boc compounds **2a–2g**.

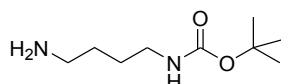
***tert*-Butyl *N*-(6-aminohexyl)carbamate (**2a**)**



Yield: 1.32 g (61%, 1.58 g/h); yellow oil

IR (neat): ν (cm⁻¹) = 3367, 1683, 1519; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 1.31 – 1.34 [m, 4H, NH₂(CH₂)₂(CH₂)₂(CH₂)₂NH], 1.43 – 1.50 [m, 13H, NH₂CH₂CH₂(CH₂)₂CH₂CH₂NH, C(CH₃)₃], 1.89 (s, 2H, NH₂), 2.68 (t, *J* = 7.0 Hz, 2H, NH₂CH₂), 3.08 – 3.10 (m, 2H, CH₂NH), 4.54 (br s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 26.47 [NH₂(CH₂)₂CH₂CH₂(CH₂)₂NH], 26.57 [NH₂(CH₂)₂CH₂CH₂(CH₂)₂NH], 28.40 [(CH₃)₃], 30.01 (CH₂CH₂NH), 33.35 (NH₂CH₂CH₂), 40.47 (CH₂NH), 41.95 (NH₂CH₂), 79.01 [OC(CH₃)₃], 155.98 (NHCO₂C); LC-MS (ESI⁺): *m/z* (%) = 217.2 (100) [M+H]⁺; HR-MS (C₁₁H₂₄N₂O₂): calc: 216.1832; found: 216.1835. Spectral data are consistent with the literature.¹

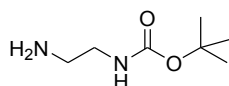
***tert*-Butyl *N*-(4-aminobutyl)carbamate (**2b**)**



Yield: 1.22 g (65%, 1.47 g/h); yellow oil

IR (neat): ν (cm⁻¹) = 3363, 2975, 2929, 1526, 1171; ¹H NMR (500 MHz, CDCl₃): δ [ppm] = 1.43 [s, 9H, (CH₃)₃], 1.45 – 1.53 [m, 4H, NH₂CH₂(CH₂)₂CH₂NH], 1.80 (s, 2H, NH₂), 2.71 (t, *J* = 6.7 Hz, 2H, NH₂CH₂), 3.10 – 3.12 (m, 2H, CH₂NH), 4.69 (br s, 1H, NH); ¹³C NMR (125 MHz, CDCl₃): δ [ppm] = 27.43 (CH₂CH₂NH), 28.40 [(CH₃)₃], 30.56 (NH₂CH₂CH₂), 40.38 (CH₂NH), 41.65 (NH₂CH₂), 79.06 [OC(CH₃)₃], 156.01 (NHCO₂C); LC-MS (ESI⁺): *m/z* (%) = 189.2 (100) [M+H]⁺; 211.2 (6) [M+Na]⁺; HR-MS (C₉H₂₀N₂O₂): calc: 188.1519; found: 188.1520. Spectral data are consistent with the literature.¹

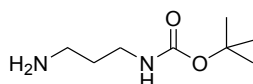
***tert*-Butyl *N*-(2-aminoethyl)carbamate (2c)**



Yield: 1.03 g (64%, 1.23 g/h); yellow oil

IR (neat): ν (cm⁻¹) = 3294, 2976, 1687, 1519; ¹H NMR (500 MHz, CDCl₃): δ [ppm] = 1.43 [s, 9H, (CH₃)₃], 2.04 (s, 2H, NH₂), 2.81 (t, J = 5.9 Hz, 2H, NH₂CH₂), 3.20 (q, J = 5.6 Hz, 2H, CH₂NH), 4.99 (br s, 1H, NH); ¹³C NMR (125 MHz, CDCl₃): δ [ppm] = 28.40 [(CH₃)₃], 40.37 (NH₂CH₂), 41.63 (CH₂NH), 79.07 [OC(CH₃)₃], 156.02 (NHCO₂C); LC-MS (ESI⁺): m/z (%) = 161.2 (100) [M+H]⁺; HR-MS (C₇H₁₆N₂O₂): calc: 160.1206; found: 160.1202. Spectral data are consistent with the literature.¹

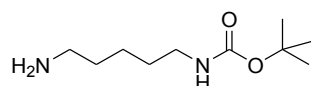
***tert*-Butyl *N*-(3-aminopropyl)carbamate (2d)**



Yield: 1.34 g (77%, 1.61 g/h); yellow oil

IR (neat): ν (cm⁻¹) = 3383, 2967, 2918, 1687, 1518, 1163; ¹H NMR (500 MHz, CDCl₃): δ [ppm] = 1.43 [s, 9H, (CH₃)₃], 1.60 – 1.64 (m, 2H, NH₂CH₂CH₂CH₂NH), 2.16 (s, 2H, NH₂), 2.76 (t, J = 6.6 Hz, 2H, NH₂CH₂), 3.19 – 3.23 (m, 2H, CH₂NH), 4.90 (br s, 1H, NH); ¹³C NMR (125 MHz, CDCl₃): δ [ppm] = 28.40 [(CH₃)₃], 33.26 (NH₂CH₂CH₂CH₂NH), 38.39 (CH₂NH), 39.61 (NH₂CH₂), 79.09 [OC(CH₃)₃], 156.15 (NHCO₂C); LC-MS (ESI⁺): m/z (%) = 175.2 (100) [M+H]⁺; HR-MS (C₈H₁₈N₂O₂): calc: 174.1363; found: 174.1361. Spectral data are consistent with the literature.¹

***tert*-Butyl *N*-(5-aminopentyl)carbamate (2e)**

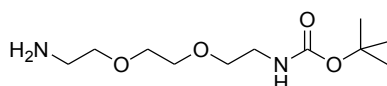


Yield: 1.19 g (59%, 1.43 g/h); yellow oil

IR (neat): ν (cm⁻¹) = 3331, 2974, 2931, 1521, 1170; ¹H NMR (500 MHz, CDCl₃): δ [ppm] = 1.33 – 1.38 [m, 2H, NH₂(CH₂)₂CH₂(CH₂)₂NH], 1.43 [s, 9H, (CH₃)₃], 1.46 – 1.52 (m, 4H, NH₂CH₂CH₂CH₂CH₂CH₂NH), 1.91 (br s, 2H, NH₂), 2.70 (t, J = 7.0 Hz,

2H, NH₂CH₂), 3.09 – 3.13 (m, 2H, CH₂NH), 4.56 (br s, 1H, NH); ¹³C NMR (125 MHz, CDCl₃): δ [ppm] = 24.01 [NH₂(CH₂)₂CH₂(CH₂)₂NH], 28.40 [(CH₃)₃], 29.86 (CH₂CH₂NH), 32.95 (NH₂CH₂CH₂), 40.46 (CH₂NH), 41.88 (NH₂CH₂), 79.04 [OC(CH₃)₃], 155.98 (NHCO₂C); LC-MS (ESI⁺): m/z (%) = 203.2 (100) [M+H]⁺; HR-MS (C₁₀H₂₂N₂O₂): calc: 202.1676; found: 202.1670. Spectral data are consistent with the literature.^I

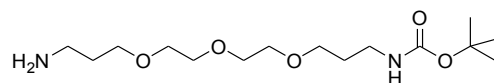
***tert*-Butyl *N*-{2-[2-(2-aminoethoxy)ethoxy]ethyl}carbamate (2f)**



Yield: 1.61 g (65%, 1.94 g/h); yellow oil

IR (neat): ν (cm⁻¹) = 3367, 1685; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 1.44 [s, 9H, C(CH₃)₃]; 1.73 (s, 2H, NH₂), 2.88 (t, *J* = 5.2 Hz, 2H, CH₂NH₂), 3.31 – 3.32 (m, 2H, CH₂NH), 3.51 – 3.55 [m, 4H, CH₂O(CH₂)₂OCH₂], 3.61 [br s, 4H, NHCH₂CH₂O(CH₂)₂OCH₂CH₂NH₂] 5.18 (br s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 28.40 [(CH₃)₃], 40.33 (CH₂NH), 41.65 (NH₂CH₂), 70.18 [NH₂(CH₂)₂O(CH₂)₂O], 70.21 (OCH₂CH₂NH), 73.25 (NH₂CH₂CH₂), 79.18 [OC(CH₃)₃], 156.02 (NHCO₂C); LC-MS (ESI⁺): m/z (%) = 249.2 (100) [M+H]⁺; 271.2 (14) [M+Na]⁺; HR-MS (C₁₁H₂₄N₂O₄): calc: 248.1731; found: 248.1729. Spectral data are consistent with the literature.^{II}

***tert*-Butyl *N*-(3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propyl)carbamate (2g)**

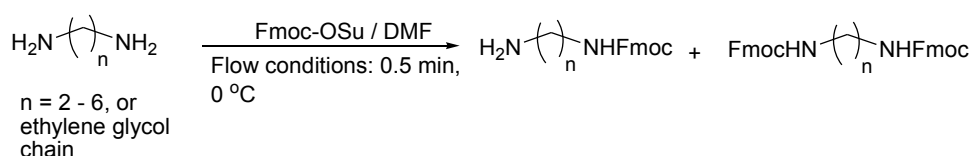


Yield: 2.15 g (67%, 2.58 g/h); yellow oil

IR (neat): ν (cm⁻¹) = 3348, 2866, 1692, 1521, 1109; ¹H NMR (500 MHz, CDCl₃): δ [ppm] = 1.42 [s, 9H, (CH₃)₃], 1.75 [quin., *J* = 6.4 Hz, 4H, NH₂CH₂CH₂(CH₂OCH₂)₃CH₂], 2.08 (s, 2H, NH₂), 2.83 (t, *J* = 6.6 Hz, 2H, NH₂CH₂), 3.20 – 3.22 (m, 2H, CH₂NH), 3.53 [t, *J* = 6.0 Hz, 2H, NH₂(CH₂)₂CH₂O], 3.55 – 3.60 [m, 6H, NH₂(CH₂)₃O(CH₂)₂O(CH₂)₂OCH₂], 3.62 – 3.64 [m, 4H, NH₂(CH₂)₃O(CH₂)₂O(CH₂)₂O], 5.1 (br s, 1H, NH); ¹³C NMR (125 MHz, CDCl₃): δ

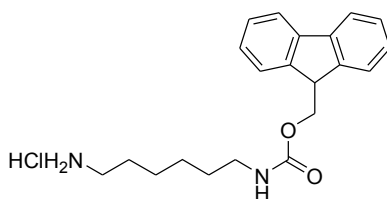
[ppm] = 28.43 [(CH₃)₃], 29.63 (CH₂CH₂NH), 32.57 (NH₂CH₂CH₂), 38.41 (NH₂CH₂), 39.61 (CH₂CH₂NH), 69.44 [NH₂(CH₂)₂CH₂O], 69.55 [OCH₂(CH₂)₂NH], 70.12 [NH₂(CH₂)₃OCH₂], 70.16 [NH₂(CH₂)₃OCH₂CH₂], 70.49 [NH₂(CH₂)₃O(CH₂)₂OCH₂], 70.53 [NH₂(CH₂)₃O(CH₂)₂OCH₂CH₂], 78.91 [OC(CH₃)₃], 156.13 (NHCO₂C); LC-MS (ESI⁺): m/z (%) = 321.2 (100) [M+H]⁺; 343.2 (5) [M+Na]⁺; HR-MS (C₁₅H₃₂N₂O₅): calc: 320.2306; found: 320.2307. Spectral data are consistent with the literature.^{III}

4. Flow Mediated Mono-Fmoc Carbamation



Diamines (0.05 M, 200 mL) and Fmoc-OSu (0.1 M, 200 mL) in DMF were fed continuously into a PTFE reactor (0.5 mm I.D., 4.0 mL total volume) immersed in an ice bath (0 °C). The reactants were fed into their respective PTFE channels (0.5 mm I.D., 0.18 mL volume) immersed in a temperature adjusted bath. The reactants converged in the T-mixer and the total flow rate of reaction stream was fixed at 8.0 mLmin⁻¹ to give a residence time of 0.5 min. The reaction stream (400 mL) was collected at steady state after 1.5 reactor volume, into a flask filled with HCl in MeOH (100 mL, -10 °C, pH 2–3) under rigorous stirring. The solution was concentrated *in vacuo* and distilled water (100 mL) was added into the crude mixture to precipitate the insoluble side product. The white solid was filtered off and the aqueous solution was washed with EtOAc (2 × 100 mL). The aqueous layer was adjusted to pH 8 with saturated NaHCO₃ solution (60 mL) and extracted with DCM (2 × 150 mL). The organic layer was washed with brine (2 × 150 mL) and dried over NaSO₄. The drying agent was filtered off and the filtrate was acidified to pH 3 using HCl in MeOH (1.25 M, 20 mL). The filtrate was concentrated *in vacuo* to give mono-Fmoc compounds **4a–4g**.

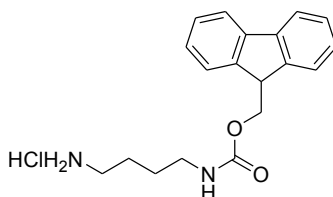
9H-Fluoren-9-ylmethyl N-(6-aminohexyl)carbamate hydrochloride (4a)



Yield: 1.69 g (45%, 2.02 g/h); off-white solid

M.p. 99 – 101°C; IR (neat): ν (cm⁻¹) = 2955, 2867, 1637, 1569, 1466, 1321, 1097; ¹H NMR (500 MHz, MeOD): δ [ppm] = 1.37 – 1.44 [m, 4H, HCl.NH₂(CH₂)₂(CH₂)₂], 1.52 (quin., J = 6.9 Hz, 2H, CH₂CH₂NHCO), 1.66 (quin., J = 7.4 Hz, 2H, HCl.NH₂CH₂CH₂), 2.91 (t, J = 7.5 Hz, 2H, CH₂NHCO), 3.11 (t, J = 6.9 Hz, 2H, HCl.NH₂CH₂), 4.20 (t, J = 6.8 Hz, 1H, CH-9), 4.36 (d, J = 6.8 Hz, 2H, CO₂CH₂CH-9), 7.31 (t, J = 7.4 Hz, 2H, CH-2 and -7), 7.40 (t, J = 7.5 Hz, 2H, CH-3 and -6), 7.65 (d, J = 7.5 Hz, 2H, CH-1 and -8), 7.81 (d, J = 7.6 Hz, 2H, CH-4 and -5); ¹³C NMR (125 MHz, MeOD): δ [ppm] = 27.20 [HCl.NH₂(CH₂)₃CH₂], 28.54 [HCl.NH₂(CH₂)₂CH₂], 30.70 (HCl.NH₂CH₂CH₂), 35.43 (CH₂CH₂NHCO), 40.72 (HCl.NH₂CH₂), 41.46 (CH₂NHCO), 67.61 (CO₂CH₂CH-9), 120.99 (CH-3 and -6), 126.17 (CH-2 and -7), 128.17 (CH-4 and -5), 128.82 (CH-1 and -8), 142.68 (CH-4a and -4b), 145.40 (CH-8a and -9a), 159.03 (NHCO₂); LC-MS (ESI⁺): m/z (%) = 339.2 (87) [M+H]⁺; 361.2 (8) [M+Na]⁺; HR-MS (C₂₁H₂₆N₂O₂): calc: 338.1989; found: 338.1983. Spectral data are consistent with the literature.^{IV}

9H-Fluoren-9-ylmethyl N-(4-aminobutyl)carbamate hydrochloride (4b)

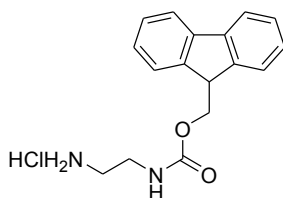


Yield: 1.77 g (51%, 2.12 g/h); off-white solid

M.p. 110 – 112°C; IR (neat): ν (cm⁻¹) = 3304, 2943, 2831, 1449, 1024; ¹H NMR (500 MHz, MeOD): δ [ppm] = 1.55 – 1.60 (m, 2H, HCl.NH₂CH₂CH₂), 1.64 – 1.70 (m, 2H, CH₂CH₂NHCO), 2.94 (t, J = 7.3 Hz, 2H, CH₂NHCO), 3.15 (t, J = 6.6 Hz, 2H, HCl.NH₂CH₂), 4.20 (t, J = 6.7 Hz, 1H, CH-9), 4.37 (d, J = 6.7 Hz, 2H, CO₂CH₂CH-

9), 7.31 (t, $J = 7.4$ Hz, 2H, **CH**-2 and -7), 7.40 (t, $J = 7.4$ Hz, 2H, **CH**-3 and -6), 7.65 (d, $J = 7.4$ Hz, 2H, **CH**-1 and -8), 7.80 (d, $J = 7.5$ Hz, 2H, **CH**-4 and -5); ^{13}C NMR (125 MHz, MeOD): δ [ppm] = 25.79 (HCl.NH₂CH₂CH₂), 27.90 [HCl.NH₂(CH₂)₂CH₂], 40.45 (HCl.NH₂CH₂), 40.92 (CH₂NHCO), 67.69 (CO₂CH₂CH-9), 120.99 (**CH**-3 and -6), 126.14 (**CH**-2 and -7), 128.17 (**CH**-4 and -5), 128.83 (**CH**-1 and -8), 142.68 (**CH**-4a and -4b), 145.36 (**CH**-8a and -9a), 159.08 (NHCO₂); LC-MS (ESI⁺): m/z (%) = 311.2 (100) [M+H]⁺; 333.2 (7) [M+Na]⁺; HR-MS (C₁₉H₂₂N₂O₂): calc: 310.1676; found: 310.1675. Spectral data are consistent with the literature.^{IV}

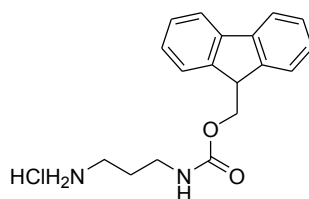
9H-Fluoren-9-ylmethyl *N*-(2-aminoethyl)carbamate hydrochloride (4c**)**



Yield: 2.01 g (63%, 2.41 g/h); off-white solid

M.p. 115 – 117°C; IR (neat): ν (cm⁻¹) = 3287, 2948, 2837, 1647, 1407, 1015; ^1H NMR (500 MHz, MeOD): δ [ppm] = 3.04 – 3.05 (m, 2H, HCl.NH₂CH₂), 3.39 (t, $J = 5.4$ Hz, 2H, CH₂NHCO), 4.23 (t, $J = 6.5$ Hz, 1H, **CH**-9), 4.42 (d, $J = 6.6$ Hz, 2H, CO₂CH₂CH-9), 7.32 (t, $J = 7.4$ Hz, 2H, **CH**-2 and -7), 7.40 (t, $J = 7.4$ Hz, 2H, **CH**-3 and -6), 7.66 (d, $J = 7.4$ Hz, 2H, **CH**-1 and -8), 7.81 (d, $J = 7.5$ Hz, 2H, **CH**-4 and -5); ^{13}C NMR (125 MHz, MeOD): δ [ppm] = 39.50 (HCl.NH₂CH₂), 41.20 (CH₂NHCO), 68.05 (CO₂CH₂CH-9), 121.01 (**CH**-3 and -6), 126.44 (**CH**-2 and -7), 128.19 (**CH**-4 and -5), 128.87 (**CH**-1 and -8), 142.70 (**CH**-4a and -4b), 145.30 (**CH**-8a and -9a), 159.42 (NHCO₂); LC-MS (ESI⁺): m/z (%) = 283.2 (90) [M+H]⁺; 305.2 (10) [M+Na]⁺; HR-MS (C₁₇H₁₈N₂O₂): calc: 282.1363; found: 282.1359. Spectral data are consistent with the literature.^V

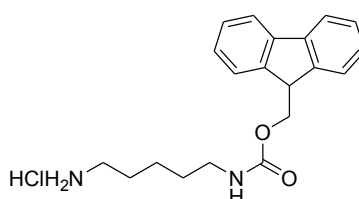
9H-Fluoren-9-ylmethyl N-(3-aminopropyl)carbamate hydrochloride (4d)



Yield: 1.96 g (59%, 2.36 g/h); off-white solid

M.p. 127 – 129°C; IR (neat): ν (cm⁻¹) = 3331, 2945, 2833, 1645, 1448, 1320, 1110; ¹H NMR (500 MHz, MeOD): δ [ppm] = 1.77 – 1.85 (m, 2H, HCl.NH₂CH₂CH₂CH₂NH), 2.91 (t, J = 7.3 Hz, 2H, HCl.NH₂CH₂), 3.21 (t, J = 6.5 Hz, 2H, CH₂NHCO), 4.21 (t, J = 6.5 Hz, 1H, CH-9), 4.42 (d, J = 6.6 Hz, 2H, CO₂CH₂CH-9), 7.32 (t, J = 7.4 Hz, 2H, CH-2 and -7), 7.40 (t, J = 7.4 Hz, 2H, CH-3 and -6), 7.64 (d, J = 7.5 Hz, 2H, CH-1 and -8), 7.80 (d, J = 7.5 Hz, 2H, CH-4 and -5); ¹³C NMR (125 MHz, MeOD): δ [ppm] = 29.26 (HCl.NH₂CH₂CH₂CH₂NH), 38.32 (HCl.NH₂CH₂), 43.64 (CH₂NHCO), 54.85 (CH-9), 67.73 (CO₂CH₂CH-9), 121.06 (CH-3 and -6), 126.11 (CH-2 and -7), 128.18 (CH-4 and -5), 128.86 (CH-1 and -8), 142.72 (CH-4a and -4b), 145.31 (CH-8a and -9a), 159.43 (NHCO₂); LC-MS (ESI⁺): m/z (%) = 297.2 (87) [M+H]⁺; HR-MS (C₁₈H₂₀N₂O₂): calc: 296.1519; found: 296.1519. Spectral data are consistent with the literature.^{VI}

9H-Fluoren-9-ylmethyl N-(5-aminopentyl)carbamate hydrochloride (4e)

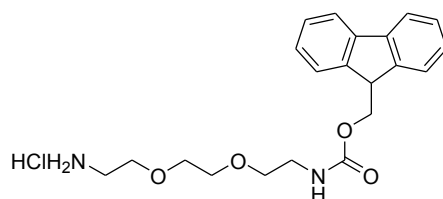


Yield: 2.24 g (62%, 2.68 g/h); off-white solid

M.p. 94 – 96°C; IR (neat): ν (cm⁻¹) = 3333, 2943, 2831, 1566, 1450, 1106; ¹H NMR (500 MHz, MeOD): δ [ppm] = 1.35 – 1.43 (m, 2H, HCl.NH₂(CH₂)₂CH₂), 1.51 – 1.57 (m, 2H, CH₂CH₂NHCO), 1.64 – 1.70 (m, 2H, HCl.NH₂CH₂CH₂), 2.91 (t, J = 7.6 Hz, 2H, CH₂NHCO), 3.12 (t, J = 6.9 Hz, 2H, HCl.NH₂CH₂), 4.20 (t, J = 6.7 Hz, 1H, CH-9), 4.37 (d, J = 6.7 Hz, 2H, CO₂CH₂CH-9), 7.31 (t, J = 7.5 Hz, 2H, CH-2 and -7), 7.40 (t, J = 7.4 Hz, 2H, CH-3 and -6), 7.64 (d, J = 7.5 Hz, 2H, CH-1 and -8), 7.80 (d,

$J = 7.5$ Hz, 2H, **CH**-4 and -5); ^{13}C NMR (125 MHz, MeOD): δ [ppm] = 24.55 [$\text{HCl}\cdot\text{NH}_2(\text{CH}_2)_2\text{CH}_2$], 28.20 ($\text{HCl}\cdot\text{NH}_2\text{CH}_2\text{CH}_2$), 30.41 ($\text{CH}_2\text{CH}_2\text{NHCO}$), 40.70 ($\text{HCl}\cdot\text{NH}_2\text{CH}_2$), 41.28 (CH_2NHCO), 43.56 (**CH**-9), 67.59 ($\text{CO}_2\text{CH}_2\text{CH}$ -9), 120.99 (**CH**-3 and -6), 126.14 (**CH**-2 and -7), 128.16 (**CH**-4 and -5), 128.82 (**CH**-1 and -8), 142.68 (**CH**-4a and -4b), 145.38 (**CH**-8a and -9a), 159.05 (NHCO_2); LC-MS (ESI^+): m/z (%) = 325.2 (74) $[\text{M}+\text{H}]^+$; HR-MS ($\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$): calc: 324.1832; found: 324.1827. Spectral data are consistent with the literature.^{IV}

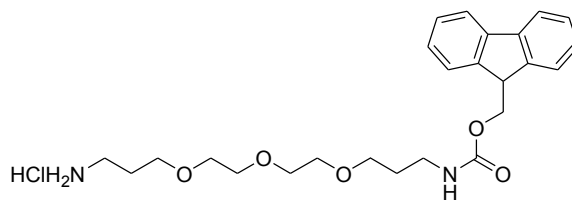
9H-Fluoren-9-ylmethyl *N*-{2-[2-(2-aminoethoxy)ethoxy]ethyl}carbamate hydrochloride (4f)



Yield: 2.48 g (61%, 2.98 g/h); off-white solid

M.p. 113 – 115°C; IR (neat): ν (cm^{-1}) = 3313, 2942, 2830, 1449, 1114; ^1H NMR (500 MHz, MeOD): δ [ppm] = 3.06 (t, $J = 5.0$ Hz, 2H, **CH**₂NHCO), 3.28 – 3.29 (m, 2H, $\text{HCl}\cdot\text{NH}_2\text{CH}_2$), 3.53 [t, $J = 5.6$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{NH}$], 3.60 – 3.67 [m, 6H, $\text{HCl}\cdot\text{NH}_2\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_2\text{O}$], 4.20 (t, $J = 6.7$ Hz, 1H, **CH**-9), 4.35 (d, $J = 6.7$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}$ -9), 7.30 (t, $J = 7.4$ Hz, 2H, **CH**-2 and -7), 7.38 (t, $J = 7.4$ Hz, 2H, **CH**-3 and -6), 7.63 (d, $J = 7.5$ Hz, 2H, **CH**-1 and -8), 7.79 (d, $J = 7.6$ Hz, 2H, **CH**-4 and -5); ^{13}C NMR (125 MHz, MeOD): δ [ppm] = 40.7 (**CH**₂NHCO), 41.6 ($\text{HCl}\cdot\text{NH}_2\text{CH}_2$), 67.8 ($\text{CO}_2\text{CH}_2\text{CH}$ -9), 67.9 ($\text{OCH}_2\text{CH}_2\text{O}$), 71.1 ($\text{OCH}_2\text{CH}_2\text{NH}$), 71.4 ($\text{HCl}\cdot\text{NH}_2\text{CH}_2\text{CH}_2$), 121.0 (**CH**-3 and -6), 126.2 (**CH**-2 and -7), 128.2 (**CH**-4 and -5), 128.9 (**CH**-1 and -8), 142.7 (**CH**-4a and -4b), 145.4 (**CH**-8a and -9a), 159.1 (NHCO_2); LC-MS (ESI^+): m/z (%) = 371.2 (100) $[\text{M}+\text{H}]^+$; 393.2 (20) $[\text{M}+\text{Na}]^+$; HR-MS ($\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_4$): calc: 370.1887; found: 370.1881.

9H-Fluoren-9-ylmethyl N-(3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propyl) carbamate hydrochloride (4g)

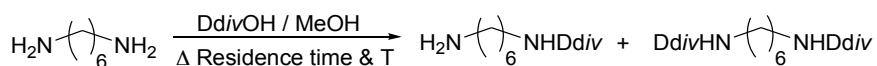


Yield: 2.44 g (51%, 2.93 g/h); off-white solid

M.p. 71 – 73°C; IR (neat): ν (cm⁻¹) = 3312, 2942, 2830, 1567, 1449, 1115; ¹H NMR (500 MHz, MeOD): δ [ppm] = 1.73 (quin., J = 6.4 Hz, 2H, CH₂CH₂CH₂NHCO), 1.88 (quin., J = 6.0 Hz, 2H, HCl.NH₂CH₂CH₂CH₂O), 3.05 (t, J = 6.4 Hz, 2H, HCl.NH₂CH₂), 3.16 – 3.20 (m, 2H, CH₂NHCO), 3.48 [t, J = 6.0 Hz, 2H, HCl.NH₂(CH₂)₂CH₂O], 3.55 – 3.63 [m, 10H, HCl.NH₂(CH₂)₃{O(CH₂)₂}₂OCH₂], 4.20 (t, J = 6.7 Hz, 1H, CH-9), 4.36 (d, J = 6.8 Hz, 2H, CO₂CH₂CH-9), 7.30 (t, J = 7.4 Hz, 2H, CH-2 and -7), 7.38 (t, J = 7.4 Hz, 2H, CH-3 and -6), 7.63 (d, J = 7.5 Hz, 2H, CH-1 and -8), 7.79 (d, J = 7.5 Hz, 2H, CH-4 and -5); ¹³C NMR (125 MHz, CDCl₃): δ [ppm] = 28. (CH₂CH₂NH), 30.9 (HCl.NH₂CH₂CH₂), 35.4 (HCl.NH₂CH₂), 39.0 (CH₂CH₂NH), 67.6 [HCl.NH₂(CH₂)₂CH₂O], 69.6 [OCH₂(CH₂)₂NH], 70.4 [HCl.NH₂(CH₂)₃OCH₂], 71.0 [HCl.NH₂(CH₂)₃OCH₂CH₂], 71.1 [HCl.NH₂(CH₂)₃O(CH₂)₂OCH₂], 71.4 [HCl.NH₂(CH₂)₃O(CH₂)₂OCH₂CH₂], 121.0 (CH-3 and -6), 126.2 (CH-2 and -7), 128.2 (CH-4 and -5), 128.9 (CH-1 and -8), 142.7 (CH-4a and -4b), 145.4 (CH-8a and -9a), 159.0 (NHCO₂); LC-MS (ESI⁺): m/z (%) = 443.3 (100) [M+H]⁺; 465.2 (11) [M+Na]⁺; HR-MS (C₂₅H₃₄N₂O₅): calc: 442.2462; found: 442.2461.

5. Flow Mediated Mono-Ddiv Enamination

Reaction Screening



1,6-diaminohexane (0.1 M, 2 mL) and DdivOH (0.1 M, 2 mL) in MeOH were fed continuously into a PTFE reactor (0.5 mm I.D., 2.0 mL total volume) immersed in an oil bath set to the desired working temperature (120 or 130 °C) and pressurised to 5

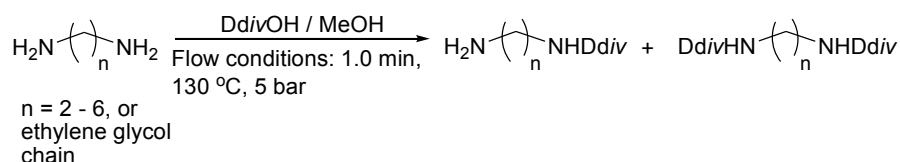
bar. The reactants were fed into their respective PTFE channels (0.5 mm I.D., 0.18 mL volume) immersed in a temperature adjusted bath. The reactants converged in the T-mixer, and the stoichiometry and residence time of the reaction were determined by adjusting the pump flow rates. The reaction stream (4 mL) was collected at steady state after 1.5 reactor volume, into a flask filled with cold MeOH (10 mL, -20 °C). An aliquot (5 µL) of the solution was collected and added to an internal standard solution (methyl benzoate, 2 mM, 200 µL) and analysed by HPLC. The individual components (product, side product and internal standard) in the solution were monitored with UV detection at 254 nm and the integrated areas of their respective peaks were obtained. The product yield and product to side product ratio were established based on the following equation:

$$\text{Conc.}_{\text{Product/Side Product}} = \frac{\text{Area}_{\text{Product/By-Product}}}{\text{Area}_{\text{IS}}} \times \frac{\text{Conc.}_{\text{IS}}}{\text{DRF}_{\text{Product/By-Product}}}$$

where DRF_{Product} (Detector Response Factor of the *N*-Ddiv compound) = 10.66

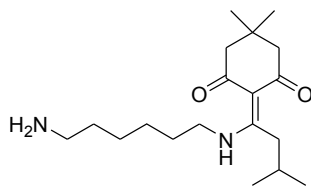
DRF_{Side Product} (Detector Response Factor of the *N,N*-Ddiv compound) = 27.82

General Procedure



Diamines (0.1 M, 100 mL) and DdivOH (0.2 M, 100 mL) in MeOH were fed continuously into a PTFE reactor (0.5 mm I.D., 4.0 mL total volume) immersed in an oil bath set at the desired working conditions (130 °C, 5 bar). The reactants were fed into their respective PTFE channels (0.5 mm I.D., 0.18 mL volume) immersed in a temperature adjusted bath. The reactants converged in the T-mixer and the total flow rate of reaction stream was fixed at 4.0 mLmin⁻¹ to give a residence time of 1.0 min. The reaction stream (200 mL) was collected at steady state after 1.5 reactor volume, into a flask filled with cold methanol (200 mL, -10 °C) under rigorous stirring. The solution was concentrated *in vacuo* and the crude mixture was purified by flash column chromatography (silica gel, 9:1 DCM–MeOH with 0.1% TEA) to give mono-Ddiv compounds **5a–5g**.

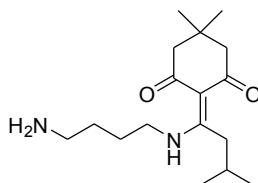
2-{1-[(6-Aminohexyl)amino]-3-methylbutylidene}-5,5-dimethylcyclohexane-1,3-dione (5a)



Yield: 1.87 g (58%, 2.24 g/h); yellow oil

IR (neat): ν (cm⁻¹) = 2955, 2867, 1637, 1569, 1466, 1321; ¹H NMR (500 MHz, CDCl₃): δ [ppm] = 0.98 [d, J = 6.7 Hz, 6H, CH(CH₃)₂], 1.02 [s, 6H, Dimedone(CH₃)₂], 1.36 – 1.53 [m, 6H, NH₂CH₂(CH₂)₃CH₂], 1.68 (quin., J = 7.0 Hz, 2H, CH₂CH₂NH), 1.95 [sep, J = 6.8 Hz, 1H, CH(CH₃)₂], 2.35 (br s, 4H, 2 x COCH₂), 2.72 (t, J = 7.0 Hz, 2H, NH₂CH₂), 2.98 [br s, 2H, (CH₃)₂CHCH₂], 3.42 (q, J = 6.4 Hz, 2H, CH₂NHC=C); ¹³C NMR (125 MHz, CDCl₃): δ [ppm] = 22.6 [CH(CH₃)₂], 26.4 and 26.7 [CH(CH₃)₂], 26.8 [NH₂(CH₂)₂CH₂], 27.1 [NH₂(CH₂)₃CH₂], 28.2 [DimedoneC(CH₃)₂], 28.9 [DimedoneC(CH₃)₂], 29.2 (CH₂CH₂NH), 29.9 (NH₂CH₂CH₂), 32.9 [(CH₃)₂CHCH₂], 37.4 (NH₂CH₂), 41.8 (CH₂NHC=C), 43.6 (COCH₂), 51.2 (COCH₂), 107.0 (NHC=C), 176.4 (NHC=C), 207.0 (2 x CO); LC-MS (ESI⁺): m/z (%) = 323.1 (100) [M+H]⁺; 345.1 (7) [M+Na]⁺; HR-MS (C₁₉H₃₅N₂O₂): calc: 323.26930; found: 323.26919.

2-{1-[(4-Aminobutyl)amino]-3-methylbutylidene}-5,5-dimethylcyclohexane-1,3-dione (5b)

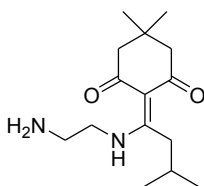


Yield: 2.12 g (72%, 2.54 g/h); yellow oil

IR (neat): ν (cm⁻¹) = 3328, 2955, 1635, 1563, 1465, 1322, 1029; ¹H NMR (500 MHz, CDCl₃): δ [ppm] = 0.98 [d, J = 6.7 Hz, 6H, CH(CH₃)₂], 1.02 [s, 6H, Dimedone(CH₃)₂], 1.60 (quin., J = 7.4 Hz, 2H, NH₂CH₂CH₂), 1.74 (quin., J = 7.4 Hz, 2H, NH₂(CH₂)₂CH₂), 1.88 (br s, 2H, NH₂), 1.96 [sep., J = 6.8 Hz, 1H, CH(CH₃)₂], 2.35 (s, 4H, 2 x COCH₂), 2.77 (t, J = 6.9 Hz, 2H, NH₂CH₂), 2.98 [br s, 2H,

(CH₃)₂CHCH₂], 3.46 (q, *J* = 6.1 Hz, 2H, CH₂NHC=C); ¹³C NMR (125 MHz, CDCl₃): δ [ppm] = 22.6 [CH(CH₃)₂], 26.7 [CH(CH₃)₂], 28.2 and 29.0 [DimedoneC(CH₃)₂], 29.9 [NH₂(CH₂)₂CH₂], 30.5 [NH₂CH₂CH₂], 37.4 [DimedoneC(CH₃)₂], 41.5 [(CH₃)₂CHCH₂, NH₂CH₂], 43.5 (CH₂NHC=C), 53.1 (2 x COCH₂), 107.0 (NHC=C), 176.4 (NHC=C), 201.7 (2 x CO); LC-MS (ESI⁺): *m/z* (%) = 295.0 (100) [M+H]⁺; 317.0 (8) [M+Na]⁺; HR-MS (C₁₇H₃₁N₂O₂): calc: 295.2380; found: 295.2382.

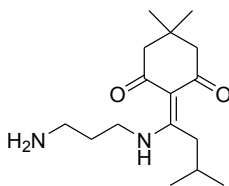
2-{1-[(2-Aminoethyl)amino]-3-methylbutylidene}-5,5-dimethylcyclohexane-1,3-dione (5c)



Yield: 2.42 g (91%, 2.91 g/h); yellow oil

IR (neat): ν (cm⁻¹) = 3355, 2956, 1632, 1565, 1028; ¹H NMR (500 MHz, CDCl₃): δ [ppm] = 0.99 [d, *J* = 6.7 Hz, 6H, CH(CH₃)₂], 1.03 [s, 6H, Dimedone(CH₃)₂], 1.51 (br s, 2H, NH₂), 1.98 [sep., *J* = 6.8 Hz, 1H, CH(CH₃)₂], 2.34 – 2.40 (m, 4H, 2 x COCH₂), 3.00 – 3.02 [m, 4H, (CH₃)₂CHCH₂, NH₂CH₂], 3.48 – 3.52 [m, 2H, NH₂CH₂CH₂NH]; ¹³C NMR (125 MHz, CDCl₃): δ [ppm] = 22.6 [CH(CH₃)₂], 28.2 and 29.0 [CH(CH₃)₂], 29.7 and 29.9 [DimedoneC(CH₃)₂], 37.6 [DimedoneC(CH₃)₂], 41.1 [(CH₃)₂CHCH₂, NH₂CH₂], 46.5 (NH₂CH₂CH₂NH), 53.4 (2 x COCH₂), 107.2 (NHC=C), 176.6 (NHC=C), 193.0 (2 x CO); LC-MS (ESI⁺): *m/z* (%) = 267.1 (100) [M+H]⁺; 289.0 (8) [M+Na]⁺; HR-MS (C₁₅H₂₇N₂O₂): calc: 267.2067; found: 267.2060. Compound has been reported in the literature as an intermediate in a sequence of reaction.^{VII} Isolation / analysis was not performed.

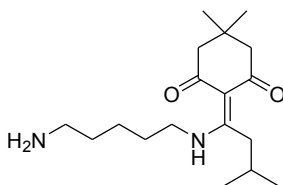
2-{1-[(3-Aminopropyl)amino]-3-methylbutylidene}-5,5-dimethylcyclohexane-1,3-dione (5d)



Yield: 2.24 g (80%, 2.69 g/h); yellow oil

IR (neat): ν (cm^{-1}) = 2957, 1638, 1567, 1466, 1318; ^1H NMR (500 MHz, CDCl_3): δ [ppm] = 0.98 [d, J = 6.7 Hz, 6H, $\text{CH}(\text{CH}_3)_2$], 1.02 [s, 6H, Dimedone(CH_3) $_2$], 1.52 (br s, 2H, NH_2), 1.82 (quin., J = 6.8 Hz, 2H, $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$), 1.97 [sep., J = 6.8 Hz, 1H, $\text{CH}(\text{CH}_3)_2$], 2.36 (s, 4H, 2 x COCH_2), 2.86 (t, J = 6.8 Hz, 2H, NH_2CH_2), 3.01 [br s, 2H, $(\text{CH}_3)_2\text{CHCH}_2$], 3.52 – 3.56 (m, 2H, $\text{CH}_2\text{NHC}=\text{C}$); ^{13}C NMR (125 MHz, CDCl_3): δ [ppm] = 22.6 [$\text{CH}(\text{CH}_3)_2$], 28.2 [$\text{CH}(\text{CH}_3)_2$], 28.9 and 29.9 [DimedoneC(CH_3) $_2$], 32.6 ($\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$), 37.3 [DimedoneC(CH_3) $_2$], 39.1 [$(\text{CH}_3)_2\text{CHCH}_2$, NH_2CH_2], 40.4 [$\text{NH}_2(\text{CH}_2)_2\text{CH}_2\text{NH}$], 41.2 (2 x COCH_2), 107.1 ($\text{NHC}=\text{C}$), 176.6 ($\text{NHC}=\text{C}$), 201.7 (2 x CO); LC-MS (ESI^+): m/z (%) = 281.1 (100) [$\text{M}+\text{H}$] $^+$; 303.0 (8) [$\text{M}+\text{Na}$] $^+$; HR-MS ($\text{C}_{15}\text{H}_{27}\text{N}_2\text{O}_2$): calc: 281.2224; found: 281.2218.

2-{1-[(5-Aminopentyl)amino]-3-methylbutylidene}-5,5-dimethylcyclohexane-1,3-dione (5e)

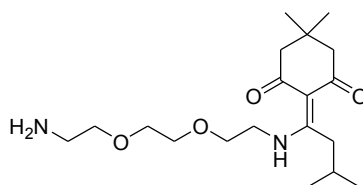


Yield: 2.22 g (72%, 2.67 g/h); yellow oil

IR (neat): ν (cm^{-1}) = 3333, 2943, 2831, 1626, 1566, 1450, 1106; ^1H NMR (500 MHz, CDCl_3): δ [ppm] = 0.98 [d, J = 6.7 Hz, 6H, $\text{CH}(\text{CH}_3)_2$], 1.02 [s, 6H, Dimedone(CH_3) $_2$], 1.44 – 1.55 (m, 4H, $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 1.70 (quin, J = 7.2 Hz, 2H, [$\text{NH}_2(\text{CH}_2)_2\text{CH}_2$], 1.88 (br s, 2H, NH_2), 1.96 [sep., J = 6.8 Hz, 1H, $\text{CH}(\text{CH}_3)_2$], 2.36 (s, 4H, 2 x COCH_2), 2.74 (t, J = 6.8 Hz, 2H, NH_2CH_2), 2.98 [br s, 2H, $(\text{CH}_3)_2\text{CHCH}_2$], 3.44 (q, J = 6.4 Hz, 2H, $\text{CH}_2\text{NHC}=\text{C}$); ^{13}C NMR (125 MHz, CDCl_3): δ [ppm] = 22.6 [$\text{CH}(\text{CH}_3)_2$], 24.2 [$\text{NH}_2(\text{CH}_2)_2\text{CH}_2$], 28.2 [$\text{CH}(\text{CH}_3)_2$], 28.9 and 29.1

[DimedoneC(CH₃)₂], 29.9 (CH₂CH₂NH), 32.7 (NH₂CH₂CH₂), 37.4 [DimedoneC(CH₃)₂], 41.7 [(CH₃)₂CHCH₂, NH₂CH₂], 43.6 (CH₂NHC=C), 51.1 (2 x COCH₂), 107.0 (NHC=C), 176.4 (NHC=C), 206.9 (2 x CO); LC-MS (ESI⁺): m/z (%) = 309.1 (100) [M+H]⁺; 331.1 (10) [M+Na]⁺; HR-MS (C₁₈H₃₃N₂O₂): calc: 309.2537; found: 309.2537.

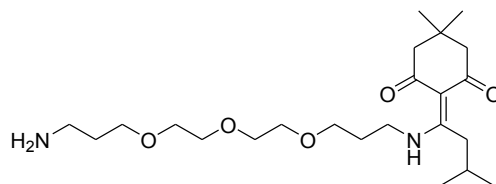
2-[1-({2-[2-(2-Aminoethoxy)ethoxy]ethyl}amino)-3-methylbutylidene]-5,5-dimethylcyclohexane-1,3-dione (5f)



Yield: 2.23 g (63%, 2.68 g/h); yellow oil

IR (neat): ν (cm⁻¹) = 3313, 2942, 2830, 1449, 1114; ¹H NMR (500 MHz, CDCl₃): δ [ppm] = 0.98 [d, J = 6.7 Hz, 6H, CH(CH₃)₂], 1.02 [s, 6H, Dimedone(CH₃)₂], 1.77 [br s, 2H, NH₂], 1.96 [sep., J = 6.8 Hz, 1H, CH(CH₃)₂], 2.36 (br s, 4H, 2 x COCH₂), 2.88 (t, J = 5.2 Hz, 2H, NH₂CH₂), 3.01 [br s, 2H, (CH₃)₂CHCH₂], 3.53 [t, J = 5.2 Hz, 2H, OCH₂CH₂NH], 3.62 – 3.63 (m, 2H, OCH₂CH₂NH), 3.66 – 3.72 [m, 6H, NH₂CH₂CH₂O(CH₂)₂O]; ¹³C NMR (125 MHz, CDCl₃): δ [ppm] = 22.6 [CH(CH₃)₂], 28.2 and 28.9 [CH(CH₃)₂], 29.7 and 29.9 [DimedoneC(CH₃)₂], 30.9 [DimedoneC(CH₃)₂], 37.4 (CH₂NHC=C), 41.7 (NH₂CH₂), 43.6 (CH₂CH₂NH), 51.2 (2 x COCH₂), 69.0 (OCH₂CH₂O), 70.3 (OCH₂CH₂O), 70.9 (OCH₂CH₂NH), 73.2 (NH₂CH₂), 107.2 (NHC=C), 176.5 (NHC=C), 207.0 (2 x CO); LC-MS (ESI⁺): m/z (%) = 355.1 (100) [M+H]⁺; 377.1 (15) [M+Na]⁺; HR-MS (C₁₉H₃₅N₂O₄): calc: 355.25913; found: 355.25914.

2-(1-Amino-17-methyl-4,7,10-trioxa-14-azaoctadecan-15-ylidene)-5,5-dimethylcyclohexane-1,3-dione (5g)



Yield: 3.03 g (71%, 3.63 g/h); yellow oil

IR (neat): ν (cm⁻¹) = 3312, 2942, 2830, 1567, 1449, 1115; ¹H NMR (500 MHz, CDCl₃): δ [ppm] = 0.98 [d, J = 6.7 Hz, 6H, CH(CH₃)₂], 1.02 [s, 6H, Dimedone(CH₃)₂], 1.75 [br s, 2H, NH₂], 1.91 – 1.98 [m, 3H, CH(CH₃)₂], NH₂CH₂CH₂], 2.35 (br s, 4H, 2 x COCH₂), 2.81 (t, J = 6.7 Hz, 2H, NH₂CH₂), 3.01 [br s, 2H, (CH₃)₂CHCH₂], 3.54 – 3.65 (m, 16H, ether bridge); ¹³C NMR (125 MHz, CDCl₃): δ [ppm] = 22.6 [CH(CH₃)₂], 28.2 and 28.9 [CH(CH₃)₂], 29.5 and 29.9 [DimedoneC(CH₃)₂], 32.9 [CH₂CH₂NH, DimedoneC(CH₃)₂], 37.1 [NH₂CH₂CH₂, (CH₃)₂CHCH₂], 39.6 (NH₂CH₂), 40.6 (CH₂NHC=C), 58.4 (2 x COCH₂), 67.6 [NH₂(CH₂)₂CH₂], 69.5 [OCH₂(CH₂)₂NH], 70.1, 70.4, 70.5 and 70.6 (ether bridge), 107.1 (NHC=C), 176.6 (NHC=C), 207.0 (2 x CO); LC-MS (ESI⁺): m/z (%) = 427.1 (100) [M+H]⁺; 449.1 (12) [M+Na]⁺; HR-MS (C₂₃H₄₃N₂O₅): calc: 427.31665; found: 427.31672.

Spectral References

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- (III) Dhar, S.; Liu, Z.; Thomale, J.; Dai, H.; Lippard, S. J. *Journal of the American Chemical Society* **2008**, 130, 11467-11476.
- (IV) Adamczyk, M.; Grote, J. *Organic Preparations and Procedures International* **1995**, 27, 239-242.
- (V) Boeijen, A.; van Ameijde, J.; Liskamp, R. M. J. *The Journal of Organic Chemistry* **2001**, 66, 8454-8462.
- (VI) Etsuko, K.; Yusuku, O.; Kazuo, K. In *Espacenet Office*, E. P., Ed. Japan, 2007; Vol. WO2007029364 (A1).
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6. Stability Study of Mono-Ddiv Protected Compounds

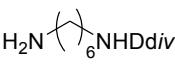
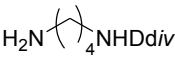
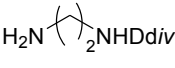
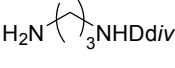
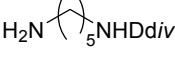
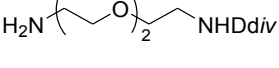
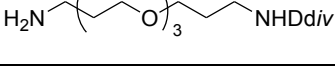
The *N*-Ddiv compounds **5a–5g** were dissolved in MeOH to give a series of solutions (1.1–2.2 mM). In general, an aliquot of the *N*-Ddiv solution (100 µL) was added to an internal standard solution (methyl benzoate, 2 mM, 400 µL) and analysed via HPLC. The mono-protected compound and internal standard were monitored with UV detection at 254 nm and the integrated areas of their respective peaks were obtained. The initial concentration of the *N*-Ddiv solution was established based on the following equation:

$$\text{Conc.}_{N\text{Ddiv}} = \frac{\text{Area}_{N\text{Ddiv}}}{\text{Area}_{\text{IS}}} \times \frac{\text{Conc.}_{\text{IS}}}{\text{DRF}_{N\text{Ddiv}}}$$

where $\text{DRF}_{N\text{Ddiv}}$ (Detector Response Factor of the *N*-Ddiv compound) = 10.66

Subsequently, the sample was heated to 80 °C for 16.5 h and re-analysed accordingly. Using the equation above, the final concentration of the mono-protected compound was calculated and in all cases, the concentrations were adjusted for the dilution factor of sample preparation. A calibration curve of compound concentration against time was plotted and the half life of the *N*-Ddiv compound was then determined from the calibration curve (Table S1).

Table S1 Solution half lives of *N*-Ddiv-diamines in MeOH at 80°C.

| Cpd. | Product | [Conc.] ⁱ _{initial} (mM) | t _{1/2} at 80°C (h) |
|------|---|---|---------------------------------|
| 5a |  | 1.4 | 25.4 |
| 5b |  | 1.6 | 12.0 |
| 5c |  | 1.6 | 8.4 |
| 5d |  | 2.2 | 8.4 |
| 5e |  | 1.5 | 15.1 |
| 5f |  | 1.8 | 9.0 |
| 5g |  | 1.1 | 12.1 |

